REMARKS

Status of the Claims

Claims 1 and 7 are pending. Claims 1 and 7 are rejected. Claims 2-6 and 8-22 are canceled. Although no claims are amended herein, Applicants provide the current status of the pending claims for the Examiner's convenience.

The 35 U.S.C. §112, first paragraph, rejection

Claims 1 and 7 are rejected under 35 U.S.C. §112, first paragraph, as the specification does not contain a written description of the claimed invention. Applicants respectfully traverse this rejection.

The Examiner states that the limitation of "from about 20 miCi/mg to about 30 mCi/mg" recited in claims 1 and 7 has no clear support in the specification and the claims as originally filed. The Examiner also states that the specification discloses support for a range from about 0.05 miCi/mg or 0.1 mCi/mg to about 100 mCi/mg (original claims 4 and 13, respectively). The Examiner concludes that nothing in the specification suggests or teaches the specific range of "from about 20 miCi/mg to about 30 mCi/mg" and that such range broadens the scope of the invention as originally disclosed in the specification. Applicants respectfully disagree.

Applicants respectfully submit that the specification discloses a plurality of specific activities for Bi-212 and Bi-213 within a range of 0.2 to 30 mCi/mg. In Figures 3A-3B, the cytotoxic effects of various doses of specific

activities of 0.2, 1, 2, 8, 10, 20, and 30 mCi/mg Bi-212 and Bi-213 (pg. 11, ll. 11 to pg. 12, ll. 8). Also, during prosecution of the instant claims amendments narrowing the range from about 0.1 to about 100 mCi/mg to about 0.1 to about 30 mCi/mg to about 10 to about 30 mCi/mg have not engendered a new matter rejection. Applicants respectfully aver that the amended, narrower recitation of "about 20 mCi/mg to about 30 mCi/mg" does not constitute new matter and does not broaden the scope of the claims as originally filed.

Applicants submit that, as Fig. 3A demonstrates a substantially equivalent cytotoxic effect for 20 mCi/mg and 30 mCi/mg, a range from about 20 mCi/mg to about 30 mCi/mg is clearly supported. The specification discloses that potency against the specific target cells depends directly on the specific activity of the labeled antibody with 30 mCi/mg being the highest (pg. 40, ll. 2-6). Also, the specification discloses that the higher 20 mCi/mg specific activity allows a mean of 10 bismuth atoms to be delivered at saturation to a cell with about 10,000 receptor sites (pg. 40, ll. 19-21).

Accordingly, in view of the arguments presented herein, Applicants respectfully request that the rejection of claims 1 and 7 under 35 U.S.C. §112, first paragraph, be withdrawn.

The 35 U.S.C. §103(a) rejection

Claims 1 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Simonson** *et al.* (1990, Can Res, 50(3 Supp:9855-9885) in view of Kasperson *et al.* (1995, Nuclear Med Comm, 16:468-476), **Vieira** *et al.* (1996,

Eur J Surgical Oncology, 22(4):331-4), and Blankenberg *et al.* (U.S. Patent No. 6,197,278), all of record, and further in view of **Kozak** et al. (1986, PNAS, USA, 83(2): 474-478). Applicants respectfully traverse this rejection.

In considering independent claim 1, the Examiner states that Simoson *et al.* teach the i.p. administration of 212-Bi labeled antibodies specific for mucin antigen TAG-72 to mice previously injected with LS1744T cells, which grows as solid tumors and ascites therein and in which solid tumors developed followed by ascites at about 20 days after injection of tumor cells (pg. 985s, 2nd col., last PP; pg. 987s, 2nd col., 1st PP). The Examiner also states that **Simonson** *et al.* disclose that the specific activity of labeled antibody is 5 to 10 mCi/mg (pg. 986s, 1st col, 2nd PP). In addition the Examiner states that **Simonson** *et al.* discloses that the tumor averages 3 gm at 13 days (Fig. 1) and that with single and repeated administration of Bi-212-antibody, 56% decrease in tumor mass is obtained (pg. 986s, 1st col., 3rd PP; Fig. 1). The Examiner further states that efficacy would be better if the antibody recognized a cell surface antigen of the target cell rather than the secreted mucin antigen TAG-72 (pg. 987s, 2nd col.).

The Examiner also states that **Simonson** *et al.* do not teach a method of killing a tumor greater than I mm in size by intravenously administering Bi-213 labeled antibodies having a specific activity from about 20 mCi/mg to about 30 mCi/mg at a dose adequate to deliver a minimum of 1 alpha track per cell. As such, the Examiner contends that although no specific teaching is found in **Simonson** *et al.* that the treated tumors are at least 1 mm in size, the tumor at 13 days weighs an average of 3 gm would be at least that size.

As such, the Examiner states that **Kaspersen** *et al.* teach that Bi-213 is an alternative to Bi-212 with the advantage of safer and easier production (pg. 475, 1st col., 1st PP). Also, the Examiner states that **Vieira** *et al.* teach that imaging of breast cancer tissues could begin 10 minutes after intravenous administration of radiolabed monoclonal antibodies (Abstract, pg. 332, 3rd PP). In addition, the Examiner states that **Blankenberg** *et al.* teach that localization of an intravenously administered targeting protein, i.e., annexin which has high affinity for anionic phospholipid surface in the target tissue, can be obtained in only a few minutes (col. 9-10). Furthermore, the Examiner states that **Kozak** et al. teach the use of Bi-212 radiolabeled antibodies to a cancer cell surface antigen, IL-2 receptor, for killing T-cell leukemia while binding to the target cells and that the specific activity of the antibody is from 1 to 40 mCi/mg (Abstract, pg. 475-476).

Thus, the Examiner concludes that it would have been prima facie obvious to one of ordinary skill in the art to substitute Bi-212 with Bi-213 and to use an antibody that targets a membrane specific antigen on cancer cells which have been successfully used in the art, as taught by **Kaspersen** *et al.* and **Blankenberg** *et al.*, respectively, in the method of treating cancer in **Simonson** *et al.* Also, the Examiner concludes that it would have been obvious to use a Bi-213 radiolabeled antibody with a specific activity higher than 10 mCi/mg taught by **Simonson** et al., such as the specific activity taught by **Kozak** et al. for optimization of the ranges of the specific activity of the antibody for immunotherapy. The Examiner notes that is within the level of ordinary skill in the art to determine optimum concentration of reactants. The Examiner also concludes it would have been obvious to an ordinary

practitioner to admininister the Bi-213-antibody intravenously one or more times, as taught by **Simonson** *et al.*, as a convenient, alternative and routine route of administration for immunotherapy because **Vieira** *et al.* and Blankenberg *et al.* teach that radiolabeled targeting compounds, including radiolabeled antibodies, reach the target cells within minutes after intravenous administration. The Examiner also concludes that one of ordinary skill in the art would be motivated to treat tumors at least 1 mm in size using a Bi-213 labeled antibody that targets a specific binding site on tumor cells with a reasonable expectation of success. Applicants respectfully disagree.

Applicants respectfully submit that **Simonson** *et al.* teach that Bi-212 may be appropriate for the treatment of peritoneal implant metastases and ascitic cancer when administered intraperitoneally as demonstrated with a Bi-212 labeled B72.3 antibody against the human colon carcinoma cell line LS174T in a murine model is examined (pg. 985s, first col., last paragraph to second col., second paragraph). The specific activity of the labeled antibody was 5-10 μCi/μg. **Simonson** *et al.* demonstrate that a single i.p. injection of 450 μCi or 3 consecutive i.p. injections of 190 μCi 13 days after tumor inoculation reduced tumor mass by 56% of well-advanced tumors averaging 3 gms in weight (pg. 986s, first col., third paragraph). In a model using smaller tumors four consecutive i.p. doses starting at day 8 of either 90 μCi or 180 μCi reduced tumor mass on average 85% with all mice in any regimen demonstrating some toxicity (pg. 986s, first col., fifth paragraph).

Kasperson *et al.* examined the cytotoxicity of Bi-213 *in vitro* and Ac-225 immunoconjugates against the human carcinoma cell lines A431 and SW1398. Bi-23 radioimmunoconjugates with a limited specific activity up to 3 μCi/μg were prepared (pg. 472, 1st col., last PP). In an in vivo spheroid model of SW1398 cells no specific cell-killing was observed using up to 1.2 μCi Bi-213 on spheroids with diameters of 0.4 mm to 0.7 mm (pg. 474, 2nd col., ll. 6-9). **Kasperson** *et al.* state that Bi-213 may have limited applicability in the treatment of solid tumors (pg. 474, last paragraph). The reference discloses that Bi^{-213} may be substituted for Bi-212 for the treatment of single cell malignancies (pg. 475, col. 1, line 3).

Vieira *et al.* teach the use of 99mTc-tetrofosmin as a gamma ray imaging agent to differentiate benign from malignant lesions in breast tissue. Imaging commences 10 minutes after injection (Abstract). However, contrary to the Examiner's statement, **Vieira** *et al.* only state that radiolabeled monoclonal antibodies are an example of a potential imaging agent already under investigation as a means of detecting breast cancer. In the Abstract **Vieira** *et al.* specifically investigate 99mTc-labeled tetrofosmin, that is 99mTc-ethoxy-ethyl phosphinoethane, which is a lipophilic, cationic chemical compound and not a radiolabeled monoclonal antibody.

Blankenberg *et al.* teach a method of imaging regions of cell death in a mammal using radiolabeled annexin V for gamma ray imaging (Abstract; col. 1, ll. 12-15). Radiolabeled annexin may be administered intravenously (col. 9, ll. 25-28) and imaging generally begins after most of the radiolabeled annexin V has localized to its target which for i.v. administration is about 30-70 minutes (col. 9, ll.

66 to col. 10, ll. 3). If the target is easily accessible such as injured blood vessels, localization may take only a few minutes (col. 10, ll. 7-13). Annexin V is not an antibody, but rather a protein isolated from tissue that binds to phosphatidylserines released from or exposed on the cytoplasmic side of cell membranes damaged due to apoptosis or necrosis of the cell.

Kozak *et al.* examined the effects of Bi-212-anti-Tac monoclonal antibody on leukemic T-cell lines in vitro and concludes that the construct is well-suited for circulating leukemic cells (pg. 478, 1st col., last sentence). Antibody specific activities of 1-40 μCi/μg, equivalent to 1-40 mCi/mg, were achieved (Abstract). Labeling the anti-Tac antibody with 2-30 μCi/μg did not significantly alter anti-Tac binding to IL-2 receptor-positive cells (pg. 475, 2nd col., 1st PP results). Concentrations of Bi-212-anti-Tac antibody delivering 6-24 rad of activity per ml reduced protein synthesis in IL-2 receptor-positive cells that bind the antibody conjugate (pg. 476, 1st col., 1st PP).

The scope of Applicants' amended claim 1 is to sequentially reduce the size of a tumor at least 1 mm in size using a selected high specific activity, i.e., 20-30 mCi/mg, bismuth-213/tumor specific antibody construct whereby a selected dose of bismuth-213/antibody saturates the targeted binding sites on an outer layer of tumor cells so that more than two atoms of Bi-213 delivers at least one alpha particle to each targeted tumor cell. Sequential removal of layers of tumor cells increase the tumor control probability, and thereby the probability of remission, in individuals having a solid tumor greater than 1 mm.

A determination of obviousness requires a teaching or suggestion of all the claim elements in the combination of cited prior art which provides motivation for one of ordinary skill in the art to make the combination with a reasonable expectation of success not found in Applicants' specification. Also, the teachings of the prior art must be considered as a whole, including that which teaches away from the claimed invention.

As primary reference, **Simonson** *et al.* do not teach or suggest a high specific activity of about 20 mCi/mg to about 30 mCi/mg for the Bi-213/antibody construct. **Simonson** *et al.* teach that Bi-212 constructs had specific activities of 5-10 μCi/μg, i.e., 5-10 mCi/mg, and disclose that 90-450 mCi were administered intraperitoneally in single or multiple doses. **Simonson** *et al.* teach that certain doses of the 5-10 μCi/μg specific activity Bi-212-GYK-DTPA-B72.3 construct decreased tumor burden and prolonged survival in some mice, although no cures were effected. **Simonson** *et al.* disclose that the reduced efficacy of the Bi-212-GYK-DTPA-B72.3 construct is due to 1) B72.3 recognizes a secreted rather than cell surface-bound antigen; 2) treatment was not begun until at least 7 days after injection of LS174T cells such that the tumor was well established; and 3) ascites developed after the development of solid LS174T tumor (pg. 987s, 2nd col., 1st PP). Thus, no suggestion to increase specific activity to the high specific activities of about 20 mCi/mg to about 30 mCi/mg as a means to increase the efficacy of Bi-212 is present in **Simonson** *et al.* and, therefore, no motivation is present for one of ordinary skill in the art to do so. The instant specification teaches that the highest

specific activities had the highest selective cell killing and as specific activity decreased, so did selectivity (pg. 29, ll. 6-13).

Combining **Kaspersen** *et al.*, **Vieira** *et al.*, **Blackenberg** *et al.* and **Kozak** *et al.*with **Simonson** *et al.* do not remedy all the deficiencies in **Simonson** *et al.* In considering **Kaspersen** *et al.* as a whole, one of ordinary skill in the art would find that **Kaspersen** *et al.* teach that Bi-213, with its safer, easier production, may be an alternative to Bi-212 for blood-borne or single cell malignancies (Abstract; pg. 475, 1st col., ll. 3-5)) and may have limited applicability for solid tumors (pg. 474, last paragraph). Applicants maintain that **Kaspersen** *et al.* teach away from treating solid tumors with Bi-213. Also, Kozak et al. teach that Bi-212 is effective against circulating leukemia cells.

In addition, Applicants respectfully submit that Bi-212 generators are different from Bi-213 generators. Kozak et al. may have achieved specific activities of 1-40 mCi/mg of Bi-212, but Applicants maintain that no combination of the cited references would lead a person having ordinary skill in this art to a reasonable expectation of success in making an amount of Bi-213 adequate to prepare the high specific activity of about 20 mCi/mg to about 30 mCi/mg Bi-213 antibody construct. Particularly, at the time of the instant invention, Kaspersen et al. were limited to specific activities of 3 μCi/μg, i.e., 3 mCi/mg, because of the amount of Bi-213 available. Therefore, one of ordinary skill in the art does not even have a reasonable expectation of success, not found in Applicants' specification, in generating the 5-10 μCi/μg, i.e., 5-10 mCi/mg, specific activity disclosed in Simonson et al. and certainly not in generating 20 mCi/mg to about 30 mCi/mg Bi-

213 antibody construct. Applicants' specification discloses that the construction of generators capable of producing 10-25 mCi of Bi-213 required several modifications of the generator disclosed in Kaspersen et al. (pg. 23, ll. 27-28).

Nor does combining **Vieira** *et al.* and **Blackenberg** *et al.* with **Simonson** *et al.*, **Kaspersen** *et al.* and Kozak et al. provide a teaching or suggestion to remedy these deficiencies. **Vieira** *et al.*, and **Blackenberg** *et al.* only disclose that various radiolabeled imaging agents or antibodies can either localize at or specifically bind to various targets within 10 to 70 min of intravenous injection. There is no teaching or suggestion, not found in Applicants' specification, present in the combination of cited prior art references that would a lead a person having ordinary skill in this art to make or use an adequate dose of a Bi-213 antibody construct having a high specific activity of about 20 mCi/mg to about 30 mCi/mg, as recited in amended independent claim 1.

In addition, the Examiner stated that determining optimum concentration of reactants and determining the dosage of the labeled antibodies recited in claim 1 is within the level of ordinary skill in the art. Applicants strongly disagree. The instant specification teaches that a minimum adequate specific activity of the radioactive construct is an integral characteristic of its description. Without this feature described, it is not possible for one of ordinary skill in the art to prepare a useful dose (pg. 12, ll. 11-14). Independent claim 1 recites that a dose of the about 20 mCi/mg to about 30 mCi/mg Bi-213 antibody construct must be selected that is effective to saturate the targeted binding sites so that more than 2 atoms of Bi-213 delivers at least one alpha particle to each targeted tumor cell.

The combination of cited references does not provide a suggestion or guidance for constructing applicants Bi-213 antibody/construct with high specific activities of the about 20 mCi/mg to about 30 mCi/mg, or for selecting a saturating dose or that saturation of the targeted sites is required to deliver more than 2 atoms for cell specific killing of the tumor cells comprising the outer layer of the solid tumor. In fact, none of the applicable references teach administering a dose of radiolabeled antibody construct of a particular disclosed specific activity to target either disseminated or solid tumor cells, but rather disclose the total μCi administered or added to the cell or spheroid cultures. Simonson et al. disclose constructs with a specific activity between 5-10 μCi/μg, **Kaspersen** *et al.* disclose constructs with a specific activity up to 3 μCi/μg and Kozak et al. disclose constructs with a specific activity between 1-40 μCi/μg, more particularly, between 2-30 μCi/μg. At best, in viewing the combination of references, Kozak et al. disclose that non-saturating doses of Bi-212-anti-Tac with specific activities of 2-30 μCi/μg will bind equivalently to IL-2 receptor-positive cells. The inference is that non-saturating doses were used to examine cytotoxic effects on IL-2 receptor positive cells.

Thus, absent a teaching or suggestion of these claim elements in the combination of **Simonson** *et al.* with **Kaspersen** *et al.*, **Vieira** *et al.*, **Blackenberg** *et al.* and **Kozak** *et al.*, no motivation is present for one of ordinary skill in the art to make the combination. Therefore, the combination of **Simonson** *et al.* with **Kaspersen** *et al.*, **Vieira** *et al.*, **Blackenberg** *et al.* and **Kozak** *et al.*cannot render amended independent claim 1 and. Furthermore, claim 7 depends directly from

amended independent claim 1. If the combination of **Simonson** *et al.* with **Kaspersen** *et al.*, **Vleira** *et al.*, **Blackenberg** *et al.* and **Kozak** *et al.*cannot render amended independent claim 1 obvious, then neither is dependent claim 7 rendered obvious by the combination.

Accordingly, in view of the claim amendment and arguments presented herein, Applicants respectfully request that the rejection of claims 1 and 7 under 35 U.S.C. §103(a), be withdrawn.

Applicants submit that claims 1 and 7, as presented herein, are in condition for allowance. Accordingly, Applicants request that claims 1 and 7 be passed to issuance. This is intended to be a complete response to the Office Action, mailed March 18, 2008. If any issues remain, the Examiner is respectfully requested to telephone the undersigned attorney for immediate resolution. Applicants believe that that fees are due for a 1 month extension of time, however, should this be in error, please debit any applicable fees from Deposit Account No. 07-1185 on which the undersigned is allowed to draw.

Respectfully submitted,

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